REMARKS

Claims 7-12, 15, 19-39 and 43-48 are pending in the present application. By this Amendment, Claims 15, 19, and 33 have been amended. No new matter has been added by these amendments.

I. Rejections

A. Rejection of Claims 20, 27, and 28 Under 35 U.S.C. § 112 First Paragraph

Claims 20, 27, and 28 are rejected under 35 U.S.C. § 112, First Paragraph for lacking "enablement for the [recited] litany of diseases and ailments". Applicant respectfully traverses this rejection.

The rejection of Claim 27 appears to be erroneous. Claim 27 does not recite diseases or ailments. Accordingly, this rejection of Claim 27 should be withdrawn.

Applicant respectfully submits that the specification is enabling for all the claimed angiogenesis dependent diseases respectively recited in Claims 20 and 28. The specification teaches that the diseases recited in the rejected claims are angiogenesis dependent diseases. As indicated in the specification, angiogenesis was known in the art at the time of the invention, and the recited diseases were known to be angiogenesis dependent. Furthermore, it is not necessary to provide experimental data on every angiogenesis dependent disease because the inhibition of angiogenesis has been shown through *in vitro* and *in vivo* testing. The data provided to demonstrate angiogenesis inhibition is sufficient for a skilled artisan to practice the invention without undue experimentation.

The specification teaches that the claimed invention can be used to treat diseases that are mediated by angiogenesis (page 13, lines 6-8) and discloses methods and compositions for treating undesired angiogenesis in a human or animal (page 13, lines 13-16; page 15, lines 11-14). Applicant discloses the specific diseases that are mediated by angiogenesis or are considered angiogenesis dependent diseases (see page 26, line 5 to page 27, line 27; page 28, lines 18-24; and page 29, lines 1-5). All of the diseases and ailments that are recited in the claims are supported in the specification.

Furthermore, angiogenesis-dependent diseases are a recognized group of diseases known in the art at the time of the invention and treatment of the angiogenesis is a therapy for all of the diseases. *Colville-Nash, P.R., et al., "Angiogenesis and Rheumatoid*

Arthritis: Pathogenic and Therapeutic Implications," Ann.Rheum.Dis. (1992) 51:919-925. In Colville-Nash, P.R., et al., it is stated that:

> "[Angiogenesis] may be beneficial as in wound healing, but may also contribute to the pathogenesis of some conditions – for example, tumor growth, neovascular glaucoma, and rheumatoid arthritis. Such diverse conditions may be grouped together as 'angiogenesis-dependent diseases,' and modulation of the angiogenic component in their pathogenesis may be used to control their progression." *See Colville-Nash*, p. 919.

Appendix A, attached hereto, cites abstracts, articles, and patents which further illustrate that each of the claimed diseases is associated with angiogenesis. Specifically, Appendix A, shows that those skilled in the art know and have known that angiogenesis plays an important role in each of the claimed diseases. The diseases taught in these references and disclosed in Applicant's specification and claims all involve angiogenesis as an underlying cause of the symptoms exhibited by the diseases.

And finally, specific experimental examples for each disease are not required in order for the specification to be enabling because the statutory requirements for a patent only require "statistically significant tests with standard experimental animals" in order to establish utility. *In re Brana* 51, F.3d at 1567, 34 USPQ.2d at 1442. In *Cross v. Iizuka*, (753 F.2d at 1051, 224 USPQ at 748), the Court stated that "a first link in the screening chain" would encourage further *in vivo* testing of the compounds and provide benefit to the public. Applicant provided results from standard *in vivo* and *in vitro* testing that demonstrate the present invention inhibits angiogenesis. Applicant also provided examples of human testing. Both are considered statistically significant tests in the art.

Undue experimentation is not required for a skilled artisan to practice the invention because, according to the Courts, enablement is not precluded by the necessity for some experimentation, such as routine screening. *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342 (Fed. Cir. 1998). "The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it's merely routine." Accordingly, it is not necessary to determine a screening test for each disease to be treated and then test the claimed compound in each screening test to determine the effectiveness of the compound against each disease. It is only necessary to determine if the compound inhibits angiogenesis. The specification of the present invention teaches inhibition of angiogensis in both *in vitro* and *in vivo* assays on pages 30-31, and in Examples I-VII. These examples provide results from rabbit cornea assays and chick

embryo chorioallantoic membrane (CAM) assays, which are standard screening tests to determine whether a compound has angiogenic inhibiting activity. Furthermore, the specification discloses dosage ranges and routes of administration and the variation of such parameters within the disclosed ranges is well within the skill of the ordinary artisan. The specification discloses representative examples of human testing and extensive data that demonstrates the inhibition of angiogenesis by the claimed compositions. Therefore, the specification is enabling for Claims 20 and 28, and undue experimentation is not required to practice the claimed invention.

For at least these reasons, Applicant respectfully requests withdrawal of the rejection.

B. Rejection of Claim 33 Under 35 U.S.C. § 112 Second Paragraph

Claim 33 is rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter. Applicant respectfully submits that the rejection is obviated in view of the foregoing amendment to Claim 33. Applicant respectfully requests withdrawal of the rejection.

C. Rejection of Claim 15 Under 35 U.S.C. §102(b)

Claim 15 is rejected under 35 U.S.C. § 102(b) as being anticipated by PCT International Publication Number WO 94/23725 to Willoughby *et al.* ("*Willoughby*"). The Office Action states that *Willoughby* teaches "a composition containing an anti-inflammatory agent and hyaluronic acid which is used to treat angiogenesis". Applicant respectfully submits that the rejection is obviated in view of the foregoing amendment to Claim 15 and requests withdrawal of the rejection.

Willoughby discloses a composition containing hyaluronic acid and anti-inflammatory agents. In contrast, the claimed invention is directed to a method for inhibiting angiogenesis in a human or animal comprising administering a composition comprising an anti-inflammatory compound and thalidomide or an analogue, hydrolysis product, or metabolite thereof.

For a reference to qualify as prior art under 35 U.S.C. § 102(b), it is well established that the reference alone must teach each and every element of the claimed invention. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 213 U.S.P.Q. 81 90 (Fed. Cir. 1986). Missing elements may not be supplied by the knowledge of one skilled in the art or the disclosure of another reference. See *Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F2d 707m 716, 223 U.S.P.Q. 1264, 1271 (Fed. Cir. 1984).

Willoughby does not teach or suggest inhibiting angiogenesis with a combination of anti-inflammatory compounds and thalidomide or its analogues, hydrolysis products, or metabolites. To the contrary, *Willoughby* is specifically directed to hyaluronic acid and non-steroidal anti-inflamatory drugs (NSAIDS) for the inhibition of angiogenesis in tumors, sub-retinal neovascularization and arthritis (page 28). *Willoughby* does not teach or suggest the element of thalidomide, or its analogues, hydrolysis products, or metabolites for the inhibition of angiogenesis. Accordingly, *Willoughby* fails to teach or suggest all the claimed elements of the present invention. Therefore, for at least these reasons, Applicant respectfully submits that amended Claim 15 is not anticipated and is allowable over the art of record. Applicant respectfully requests withdrawal of this rejection.

D. Rejection of Claims 7-12, 125, 19-39 and 43-48 Under 35 U.S.C. §103(a)

Claims 7-12, 15, 19-39 and 43-48 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Oliver *et al.* Abstracts of Scientific Presentations; June 1995; 38 No. 6 ("*Oliver*") in view of either *Willoughby* (WO 94/23725) or Collville-Nash *et al.* Annals of Rheum. Dis. 1992; 51: 919-925 ("*Collville*"). Applicant respectfully traverses the rejection.

The Office Action states that *Oliver* teaches thalidomide and its analogs for treating inflammatory synovitis and that these benefits might be related to modulation of angiogenesis. The Office Action also states that *Willoughby* teaches a composition containing an anti-inflammatory agent and hyaluronic acid to treat angiogenesis, and further that *Collville* teaches the administration of steroids to modulate angiogenesis. The Office Action concludes that a skilled artisan "would have been motivated to combine these prior art teaches (sic) especially since each are directed to treating the same ailment, specifically angiogenesis".

The determination of obviousness under 35 U.S.C. § 103 is a legal conclusion based on factual evidence. *Burlington Indus., Inc. v. Quigg*, 822 F.2d 1581, 1584, 3 U.S.P.Q.2d 1436, 1439 (Fed. Cir. 1987). The prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated one of ordinary skill in the art to modify a reference or to combine references. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Further, the prior art reference or combination of references must teach or suggest all the limitations of the claims. See *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). To support a conclusion

of obviousness, "either the references must expressly or impliedly suggest the claimed combination or the [PTO] must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 U.S.P.Q. 972, 973 (Bd. Pat. App. & Int. 1985). In evaluating obviousness, the Federal Circuit made it very clear that one must look to see if "the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success viewed in light of the prior art." *In re Dow Chemical Co. v. American Cyanamid Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

Furthermore, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). A statement that modifications of the prior art to meet the claimed invention would have been well within the ordinary skill of the art at the time the claimed invention was made because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat & Inter. 1993). Furthermore, the level or skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

Applicant respectfully asserts that the line of reasoning expressed in the Office Action does not make a *prima facie* showing of obviousness. *Oliver* in view of either *Willoughby* or *Collville* fails to teach or suggest all the claimed limitations of Applicant's claimed invention. Furthermore, *Oliver* in view of either *Willoughby* or *Collville* fails to provide suggestion or incentive to combine the teachings.

Oliver appears to indicate that thalidomide and its analogs may be effective in treating inflammatory synovitis and that these benefits might be related to modulation of angiogenesis. *Willoughby* is explained in detail above and incorporated here for purposes of brevity. *Collville* appears to indicate that indomethicin inhibits angiogenesis in the rat cornea, and that dexamethasone does **not** show angiogenesis inhibition.

In contrast, the claimed invention as set forth in Claims 7, 26 and 27 is directed to compositions and methods for inhibiting angiogenesis or treating angiogenesis dependent diseases in a human or animal. The claimed invention employs a composition that comprises the combination of an anti-inflammatory compound and an angiogenesis inhibiting compound. The angiogenesis inhibiting compound is identified by claimed structures which are further specified by Markush groups. These Markush groups have

various constituents that can be substituted to include thalidomide and analogues, metabolites, or hydrolysis products of thalidomide.

As explained above, *Oliver* is limited to thalidomide for the inhibition of angiogenesis associated with inflammatory synovitis. *Willoughby* is limited to the use of hyaluronic acid and NSAIDS. *Willoughby* does not teach or suggest the substitution of hyaluronic acid with any other angiogenesis inhibiting compound, including the claimed angiogenesis inhibiting compounds. Nor is there any motivation in *Oliver* to combine anti-inflammatory drugs with any compound falling within the scope of the claimed structures of the rejected claims. Since neither *Oliver* nor *Willoughby* teach or suggest combining anti-inflammatory compounds with any compound falling within the scope of the claimed structures of the rejected claims, *Oliver* in view of *Willoughby* fails to teach every element of the claimed invention of the rejected claims.

As stated above, *Collville* teaches that indomethicin inhibits angiogenesis in the rat cornea, and that dexamethasone does **not** show inhibition of angiogenesis. *Collville* is limited solely to the anti-inflammatory drug, indomethicin, for inhibiting angiogenesis. *Collville* does not teach or suggest compositions comprising compounds falling within the scope of the claimed structures of the rejected claims. Further, *Collville* does not teach or suggest combining ant-inflammatory compounds with anti-angiogenesis inhibiting compounds. Thus one of ordinary skill in the art would not look to the teachings of *Collville* to combine with the teachings of *Oliver.* Therefore, since neither *Oliver* nor *Collville* teach or suggest combining an anti-inflammatory compound with ithe claimed angiogenesis inhibiting compounds, *Oliver* in view of *Collville* fails to teach every element of the claimed invention of the rejected claims.

Applicant respectfully submits that Claims 7, 26, and 27 are patentable over *Oliver* in view of either *Willoughby* or *Collville.* Accordingly, Applicant respectfully requests withdrawal of this rejection.

Furthermore, because Claims 8-12, 15, 19-25, 28-39 and 43-48 recite additional features and depend from Claims 7, 26, and 27, these claims are also allowable over the art of record. Applicant respectfully requests withdrawal of this rejection.

II. Conclusion

Applicants respectfully submit that Claims 7-12, 15, 19-39 and 43-48 are free of the prior art of record and accordingly request allowance of the application.

Should the Examiner believe that anything further is necessary to place the application in better condition for allowance, the Examiner is respectfully requested to contact Applicant's representative at the telephone number listed below.

No fees are believed due, however, the Commissioner is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Deposit Account No.11-0855.

Respectfully submitted,

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